EXHIBIT "A"

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-592

Eli Lilly and Company
Attention: Timothy R. Franson, M.D.
Lilly Corporate Center
Indianapolis, IN 46285

SEP 30 1996

Dear Dr. Franson:

Please refer to your September 22, 1995, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) 2.5 mg, 5 mg, 7.5 mg, and 10 mg Tablets.

We acknowledge receipt of your amendment of September 16, 1996.

This new drug application provides for a new chemical entity indicated for the treatment of the manifestations of psychotic disorders.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in your submission of September 16, 1996. Accordingly, the application is approved effective on the date of this letter.

As discussed during the September 17, 1996, working meeting (telecon) with the Division, and as amended in several follow-up faxes and telephone conversations, the draft labeling was revised and is included as an attachment to this approval letter. These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-592. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

ZY 879 395

TRF OCT 15 1996

We remind you of your Phase 4 commitment, specified in the submission of September 16, 1996, to conduct a relapse prevention study to evaluate the safety and effectiveness of olanzapine in long-term use. Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitment, please submit protocol, data, and final reports to this NDA as correspondences. For administrative purposes, all submissions, including labeling supplements, relating to Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

CDR Steven D. Hardeman, R.Ph.
Project Manager
(301) 594-5533

Sincerely yours,

Robert Temple

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

attachment

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 20-592/S-006
NDA 20-592/S-008

Food and Drug Administration
Rockville MD 20857

Eli Lilly and Company, Inc.
Attention: Greg Brophy, Ph.D.
Lilly Corporate Center
Indianapolis, IN 46285

MAR 17 2000

Dear Dr. Brophy:

Please refer to your resubmitted supplemental new drug application (S-006) dated December 22, 1999, received December 23, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzepine) tablets, 2.5, 5, 7.5, 10 and 15 mg. This submission constituted a complete response to our October 28, 1999 action letter. We also acknowledge receipt of your submissions dated November 23, 1999, February 18, 2000, February 25, 2000 and February 29, 2000. In addition we refer to discussions which have taken place between representatives of your firm and this Agency on February 22, 2000 (teleconference), February 23, 2000 (meeting), and February 28, 2000 (teleconference).

Please also refer to your supplemental application S-008, submitted August 26, 1998, received August 27, 1998.

Supplemental application S-006 proposes the use of olanzapine in the treatment of manic or mixed episodes in bipolar disorder. Supplemental application S-008 provides for revisions to the "Geriatric Use" subsection of the package insert for ZYPREXA® (olanzapine) Tablets in compliance with the Federal Register Notice of August 27, 1997.

We have completed the review of resubmitted supplemental application S-006 as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text (please refer to the enclosed package insert text). Accordingly, supplemental application S-006 is approved, effective on the date of this letter.

Please note that your acceptance, and our approval, of the agreed upon labeling text for S-006 includes labeling changes in the "Geriatric Use" subsection which relate to 008. We therefore consider S-008 to be superseded by the approval of S-006; we will not review this application, but it will be retained in our files. We note your concurrence with this action as indicated by your communication of February 29, 2000 cited above.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL, as soon as it is available, in no case more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved sNDA number 20-592/S-006". Approval of this submission by FDA is not required before the labeling is used.

Please also submit one market package of the drug product when it is available.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product in the newly approved indication. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this supplemental NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

You have been advised that the Pediatric Final Rule (63 FR 66632) requires that all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that your Proposed Pediatric Study Request was submitted to this supplemental NDA on February 25, 2000 and received February 28, 2000. A formal Written Request will be forwarded to you under separate cover.

Also, as you know, on February 2, 1999, the financial disclosure rule, published in the Federal Register of February 2, 1998, became effective. Although your supplemental NDA was submitted before this rule was in effect, for any covered clinical studies submitted after February 2, 1999 which relate to this supplement, the regulations require financial information on clinical investigators conducting those trials. Please note that this requirement also applies to pediatric studies conducted in accordance with the Pediatric Final Rule. For further information about this requirement, you may

contact Ms. Linda Carter, Associate Director, Regulatory Affairs, Office of Drug Evaluation I at 301.594.6758.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions concerning this supplemental NDA, please contact Doris J. Bates, Ph.D., Regulatory Project Manager, at (301) 594-5536.

Sincerely yours,

Russell Katz, MD
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and
Research

Attachment (agreed-upon package insert text)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-592 / S-019

Eli Lilly and Co., Inc.
Attention: Gregory T. Brophy, Ph.D.
Lilly Corporate Center
Indianapolis, Indiana 46285
USA

Dear Dr. Brophy:

Please refer to your supplemental new drug application (NDA) dated November 20, 2002, received November 21, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) Tablets, 2.5, 5, 7.5, 10, 15, and 20 mg. This supplemental NDA provides for the use of olanzapine in the long-term treatment of bipolar I disorder.

We also acknowledge receipt of your amendments dated November 4, 2003 and November 13, 2003. Your submission of November 13, 2003 constituted a complete response to our September 22, 2003 action letter.

Application approved. We have completed the review of this application as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text, per our discussions of January 13, 2004.

Final Printed Labeling. The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Please submit the FPL electronically, according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-592/S-019". Approval of this submission by FDA is not required before the labeling is used.

Waiver of Requirement for Pediatric Studies. All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for the use of olanzapine in the long-term treatment of bipolar I disorder.

No Postmarketing Commitments Required. We note that there are no postmarketing commitments for this supplemental application.

Promotional Materials. In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising and Communications (DDMAC), HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Healthcare Professional Letters. If you issue a letter communicating important information about this drug product (i.e., a "Dear Healthcare Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please contact Doris J. Bates, Ph.D., Regulatory Project Manager, at 301-594-2850, or via e-mail at batesd@cder.fda.gov.

Sincerely,

(See appended electronic signature page)

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure (Agreed-Upon Labeling) [The electronic signature page will follow the labeling.]

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
1/14/04 12:48:23 PM